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Gold Nano Particles of Cancer Treatment: A Review

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ABSTRACT

Gold nanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photothermal agents, contrast agents and radiosensitise. Cancer is the disease caused by an uncontrolled division of abnormal cells in a part of the body. In this review some various nanotechnology is found the 10 new technique and treated with all the cancer treatment is beneficial compare to other cancer therapy. Will the synthesis of various gold nano particles and find out the gold nano shells, gold nano cages, gold colloidal nano spheres. Then Nanoparticles can be used to target bio-markers or antigens that are highly specific to Cancer cells. This gold nano particles using the therapy Rheumatoid arthritis, Alzheimer's disease, Cancer detection. The introduces to the cancer diseases, nano particles techniques, cancer therapy, then various types of the gold nano particles, properties of cancer cells, future scope of cancer treatment, applications, background of cancer treatment will be discussed.

Keywords: Gold nano particles techniques, cancer treatment, clinical trials.

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INTRODUCTION

Gold nanoparticles are emerging as promising agents for cancer therapy and are being investigated as drug carriers, photothermal agents; contrast agents and radio sensitizers. Nanoparticles are microscopic particles that have at least one dimension within a scale of 1-100 nanometres. Gives a clearer picture of that scale by comparing the nanoscale to macroscale objects. The term “nanoparticle” refers to a combination of individual atoms. For example, a gold nanoparticle may be made up of 50 individual gold atoms. Contrary to popular belief, nanoparticles are not necessarily spherical in shape. They can be rods, pyramids, spheres, or unnamed shapes. Whatever shape they may be, the cluster of particles is denoted as one particle because the traits of the nanoparticle as a whole are important in determining properties and reactivity.

Colloidal gold, also known as "nanogold", is a suspension (or colloid) of sub-micrometre-sized particles of gold in a fluid — usually water. The liquid is usually either an intense red colour (for particles less than 100 nm), or a dirty yellowish colour (for larger particles). “Gold nanoparticles are very good at scattering and absorbing light,” It has scattering property in a living cell to make cancer detection easier.

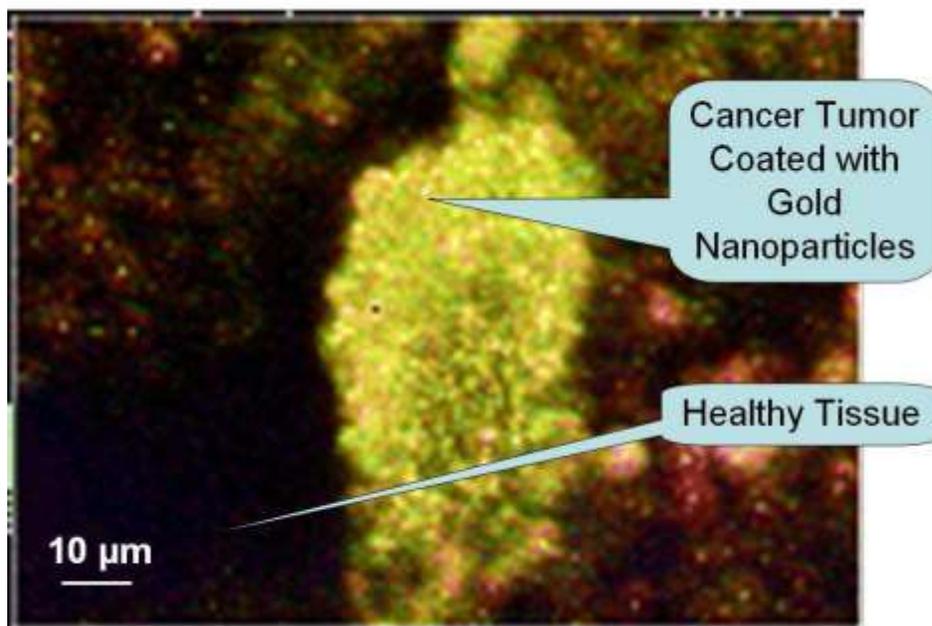
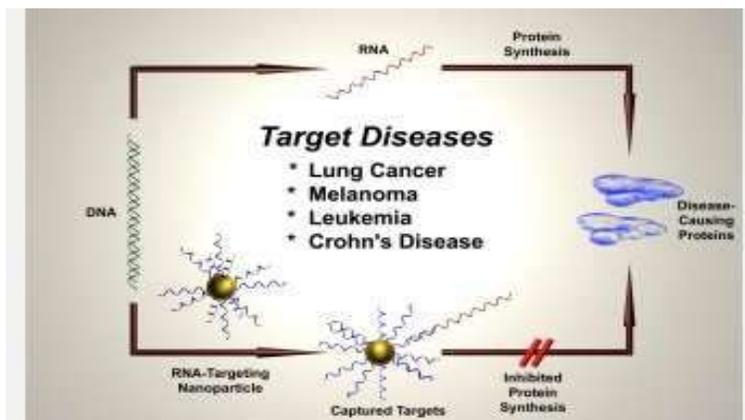


Figure 1: Cancer Tumor Coated With Gold Nanoparticles

Many cancer cells have a protein, known as Epidermal Growth Factor Receptor (EGFR), all over their surface, while healthy cells typically do not express the protein as strongly. By conjugating, or binding, the gold nanoparticles to an antibody for EGFR, suitably named anti-EGFR. It is able to get the nanoparticles to attach themselves to the cancer cells. “If you add this conjugated nanoparticle solution to healthy cells and cancerous cells and you look at the image, you can tell with a simple microscope that the whole cancer cell is shining,” “The healthy cell doesn’t bind to the nanoparticles specifically, so you don’t see where the cells are. With this technique, if you see a well defined cell glowing, that’s cancer”

The gold nanoparticles have 600 percent greater affinity for cancer cells than for noncancerous cells. The particles that worked the best were 35 nanometers in size. Technique using cell cultures of two different types of oral cancer and one non-malignant cell line. The shapes of the strong absorption spectrum of the gold nanoparticles are also found to distinguish between cancer cells

and noncancerous cells. Another benefit is that the results are instantaneous. “If you take cells from a cancer stricken tissue and spray them with these gold nanoparticles that have this antibody you can see the results immediately. The scattering is so strong that you can detect a single particle,” Finally, the technique isn’t toxic to human cells. A similar technique using artificial atoms known as Quantum Dots uses semiconductor crystals to mark cancer cells, but the semiconductor material is potentially toxic to the cells and humans. “This technique is very simple and inexpensive to use”. It making cancer detection easier, faster and less.

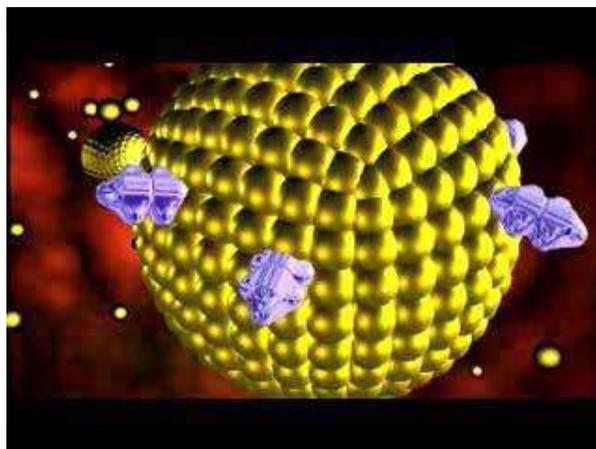


Figure 2-A gold nanoparticle is made of individual gold atoms

Cancer²

Cancer is the disease caused by an uncontrolled division of abnormal cells in a part of the body.

Advantages^{3,4}

The growing evolution of nanotechnology has opened up doors to scientists demonstrating a vast array of advantageous uses nanotechnology has to offer in the area of medicine. A perfect example is the new concept of using nanorods to detect cancer; this has proved to have numerous positive outcomes compared to flow cytometry, in which fluorescent markers bind to cancer cells. The price of diagnosis compared to that of the method of flow cytometry could be cut by two-thirds just by using nanorods. Where flow cytometry demands a larger sample size, nanorods only require a fraction of the number of cells, meaning that nanorods are capable of helping to determine an earlier diagnosis. Even more so, nanorods have been proven to be far less invasive compared to some other methods due to the fact nanorods use blood samples and do not require a biopsy. However, it must be taken into consideration that some forms of cancer are not expressed in blood samples and in such cases other methods would be necessary to detect cancer. The added advantage of this is that scientists can use conventional microscopes and light sources to view the

samples versus other methods that utilize expensive microscopes or lasers contributes to the overall cost savings of nanorods.

Protects drugs from being degraded in the body before they reach their target. Enhances the absorption of drugs into tumors and into the cancerous cells themselves. Allows for better control over the timing and distribution of drugs to the tissue, making it easier for oncologists to assess how well they work. Prevent drugs from interacting with normal cells, thus avoiding side effects.

Disadvantages

Yet in recent times growing numbers of scientists have begun to shine a light on the possible concerns that nanoparticles bear and their negative health effects. Nanoparticles are famous for their small size. Due to this, it is possible for nanoparticles to penetrate almost any membrane in the body. Where this is advantageous for cancer treatment, it is a major drawback because of the potential harm to healthy cells and DNA – causing more cancer cells. Careful consideration must also be taken concerning the disposal techniques for nanoparticles used in manufacturing or other processes. It is important that special disposal methods are practiced to stop damaging particles from ending up in the water supply or in the general environment, where they would be impossible to track.

Another potential disadvantage derived from nanoparticles is concerns over the idea of mass poisoning.⁹ As nanotechnology can be found in almost every food product in the market place, it is a probable idea that the future health effect of this has the potential to be on a large scale. If the coatings contain toxic nanoparticles which are capable of transgressing the blood-brain barrier, they then run the risk of creating mass poisoning. Atomic weapons can now be more accessible and made to be more powerful and more destructive. These can also become more accessible with nanotechnology.

Since these particles are very small, problems can actually arise from the inhalation of these minute particles, much like the problems a person gets from inhaling minute asbestos particles. Presently, nanotechnology is very expensive and developing it can cost you a lot of money. It is also pretty difficult to manufacture, which is probably why products made with nanotechnology are more expensive.

Nanoparticles Techniques^{3,4}

1. Liposome Nanoparticles

Lipids form nanoparticle vesicles through the self-assembly of amphiphilic lipids and excipients. The lipids form a bilayer based on hydrophobic interactions in continuous parallel packing, with the hydrophilic head groups positioned towards the aqueous environment. Hydrophilic molecules

can be encapsulated in the inner aqueous phase while hydrophobic molecules can be carried in the hydrophobic domains of the lipid bilayer. Physicochemical properties of liposomes can be precisely changed to control surface charge, functionality, and size by simply mixing commercially available lipid molecules. This offers a significant advantage over other carriers that require much more controlled synthesis steps and additional chemical modifications. Generally, lipids used to prepare vesicular formulations are found in the human body and approved by the FDA, such as DSPE (1,2-distearoylsn-glycero-3 phosphoethanolamine), HSPC (hydrogenated phosphatidylcholine from soybean lecithin), Egg PG (egg yolk phosphatidylglycerol) and DSPC(1,2-distearoyl-glycero-3-phosphocholine). Each of these lipids can be obtained with or without PEG, which can be used to modify the surface of the resulting liposome.

Doxil, a PEGylated liposome clinically used to treat multiple Liposomal formulations have demonstrated multiple benefits as drug delivery vehicles. However, they must be used to carry very potent drugs due to their low encapsulated load. Lipid-based vesicles pose several other challenges such as instability in the bloodstream, poor solubility of many drugs in the lipid/surfactant solution, and a rapid, burst release of drug. Liposomal formulations are also associated with severe side effects due to their accumulation in skin tissue. While prolonged drug release kinetics are difficult to control using liposomal systems, alternatives such as environmentally triggered release can be easily engineered by inserting destabilizing lipids with amine head groups into the vesicle membrane or including additives such as morphine in the lipid formulation . There are currently no liposomal formulations with triggered drug release approved for clinical use or in early phases of clinical trials. However, LiPlasome Pharma developed on-targeted liposomes consisting of lipids designed to be degraded by phospholipaseA2 (PLA2), which is up-regulated in the tumor microenvironment.

The lipid degradation products are converted into anticancer drugs, resulting in local delivery of cytotoxic drugs in the tumor. In-vivo results showed a delay in colon cancer progression using a human tumor xenograft mice model This approach also provides the possibility of multi-drug delivery. Protein stabilization of liposomes is being investigated by Azaya Therapeutics to deliver hydrophobic drugs such as docetaxel for cancer therapy. Docetaxel is encapsulated into the liposome bi-layer and stabilized by albumin to prevent rapid drug leakage (ATI-1123). The results of ATI-1123 efficacy studies in human xenograft mice models for prostate, pancreatic, and non-small-cell lung cancer (NSCL cancer) showed partial tumor regression in 90% of the PC3 tumor xenograft model and improved efficacy in the pancreas model when compared to groups treated

with docetaxel at equal doses (25 mg kg⁻¹). This may be explained by the slower plasma elimination and higher.

2. Polymer–Drug Conjugates Nanoparticles

Polymer–drug conjugates are one of the most investigated types of nanocarriers and are currently in clinical trials as advanced as phase III. Polymer–drug conjugates are formed through side-chain grafting of drugs to polymer chains, allowing them to deliver high doses of chemotherapeutic drugs. Although the physicochemical properties of a number of formulations are not disclosed, the size of polymer–drug conjugates is generally below 20 nm. HPMA-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer (PK1) was the first synthetic polymer–anticancer drug conjugate to enter clinical trials more than a decade ago and the clinical phase II trial for women with advanced breast cancer is still on going. Similarly, Prolindac (AP5346) is composed of a HPMA backbone copolymer with platinum grafted to the side chains through a pH-sensitive chelate or designed for drug release in the tumor environment. Preclinical data shows superior efficacy of the polymer–drug conjugates using multiple cancer models including a M5076 sarcoma platinum-resistant tumor xenograft mice model, multiple colon xenograft models, L1210 leukemia, and 0157 hybridoma models.

Oxaliplatin drug loading was ~10% (w/w) using a polymer chain of 25 kDa and the drug release was slow. Formulations were injected once a week for three weeks and the polymer–drug conjugates significantly retarded tumor growth over one month due to higher intracellular concentration of Pt. In the clinical phase I trial conducted in Europe, systemic injection of 640 mg Pt m⁻² weekly for 3 weeks resulted in a response by platinum-resistant ovarian cancer. Recently, Access Pharmaceuticals Inc. reported the results of the clinical phase II trial showing that 66% of the patients with ovarian cancer experienced meaningful disease stabilization and limited side effects.

Polyamino acids grafted with drugs on the side chains are another class of polymer–drug conjugates that have demonstrated high drug loading and efficacy. In the case of polyglutamate-glycine-camptothecin (CT-2106), degradable linkers have allowed drug loadings ranging from 5% to 50%. Using a glycine linker, drug loadings were increased threefold over polyglutamate-camptothecin alone due to reduced steric hindrance. However, a formulation with a drug load of ~30% was selected for clinical trials due to superior stability and efficacy in human tumor xenograft mice models. Meanwhile, Xyotax, a similar polymer–drug conjugate (polyglutamate-paclitaxel), is in 22 clinical trials at the moment for multiple cancer therapies including prostate cancer, metastatic breast cancer, neck cancer, metastatic colorectal cancer, and recurrent NSCL

(Phase III). Paclitaxel is grafted to polyglutamic acid (30–40 kDa) to reach a drug load of 20–40% by weight. The clinical data shows an improvement in median survival in Xyotax patients compared with the control group, although there were no differences in the overall survival. One benefit of the treatment was the reduction of multiple side effect including neurotoxicity. Overall, polymer–drug conjugates are considered simple nanocarrier systems, but tuning the optimal formulation might require extensive development. For example, small changes in the polymer–drug conjugation efficiency may significantly modify the pharmacokinetic parameters and tissue biodistribution.

3. Polymeric Nanoparticles

Polymeric nanoparticles may represent the most effective nanocarrier for prolonged drug delivery. The early in vitro and in vivo development of polymeric nanoparticles loaded with drugs in the 1980s using polyalkylcyanoacrylate-based nanoparticles releasing doxorubicin led to multiple reports using polymer-based materials for drug delivery. Langer and Folkman demonstrated the first controlled release of macromolecules using polymers, which allowed the development of anti-angiogenic drug delivery systems for cancer therapy and opened new areas for the delivery of macromolecules. In 1994, Langer et al. described nanoparticles composed of poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) and PEG block copolymer as “long-circulating nanoparticles” due to their stealth properties, leading to an interest in polymeric nanoparticles and their therapeutic applications. Only a few papers per year were published using polymeric nanoparticles as a drug delivery system in the 1990s in contrast to ~200 papers in 2008. Polymeric nanoparticles provide significant flexibility in design because polymers can be biodegradable or non-biodegradable, and can be made synthetically or derived from natural sources. Some common polymers used for nanoparticle formation include poly(lactic acid) (PLA), dextran, and chitosan. Biodegradable polymers are typically degraded into individual monomers, which are metabolized and removed from the body via normal metabolic pathways. Degradation and drug release kinetics can be precisely controlled by the physicochemical properties of the polymer, such as molecular weight, dispersity index, hydrophobicity, and crystallinity. In general, drugs can be released in a controlled manner with first-order kinetics due to drug diffusion through the polymeric matrix or triggered in response to the local environment. The nanoparticle surface is usually statically stabilized by grafting, conjugating, or adsorbing hydrophilic polymers such as PEG to its surface, which can also reduce hepatic uptake and improve circulation half-life.

4. Micelle Nanoparticles

Micelles are composed of lipids or other amphiphilic molecules, such as polymers or polyamino acids, and self-assemble into small nanoparticles composed of a hydrophobic core. Micelles have been developed as drug delivery carriers for hydrophobic drugs ; . There are multiple examples of micellar formulations under investigation or in clinical trials, such as Genexol-PM ;, NC-6004 , NK105 , and the NK91. Genexol-PM is the first non targeted polymeric micellar formulation approved for cancer therapy. It was approved in Korea in 2006 as a first-line therapy for metastatic breast and NSCL cancer (currently in Phase III). It is currently being evaluated in a clinical phase I. trial in the USA for metastatic pancreatic cancer therapy. Genexol-PM is composed of a block copolymer PDLLA (1.75 kDa)–mPEG (2 kDa) forming micelles with a size of ~60 nm and paclitaxel loading of ~15% (w/w). The maximum tolerated dose(MTD) of Genexol-PM is threefold higher than Taxol (60 mg kg₋₁ vs. 20 mg kg₋₁, respectively) and the median lethal tolerated dose (LD50) using Sprague–Dawley rats was reported to be ~20 times higher than Taxol. Interestingly, the area under the plasma concentration (AUC) was similar for both formulations. However, paclitaxel had more significant accumulation in tissues such as the liver and tumor with the Genexol-PM formulation, leading to differential tumor cytotoxicity and reduction of tumor volume . Results of a clinical phase I trial showed that while the MTD was almost double (390 mg m₋₂) for Genexol-PM compared to Taxol with similar toxicological profiles, the recommended dose was determined to be 300 mg m₋₂ . The clinical phase II trial in Korea evaluated Genexol-PM as a co-therapy with cisplatin for advanced NSCL in contrast to a single agent therapy . The clinical phase II results showed ~30% of the patients had stable disease status and 60% of the patients had an increased survival of one year using slightly lower doses of cisplatin than with the combined treatment of Taxol with cisplatin (60 mg m₋₂ versus 75 mg m₋₂, respectively) Other companies such as Labopharm and Intezym are also developing micelle systems for the delivery of a myriad of anticancer agents using formulations with sizes ranging from 10 to 200 nm using polyamino acids.

5. Dendrimer Nanoparticles

Dendrimers are globular macromolecules (5–10 nm) with well-defined branching architectures and surface functional groups available for further modification. The multifunctional capabilities possible through controlled synthesis methods are leading to new classes of dendrimers that can carry drug molecules, diagnostic agents, and targeting molecules. Dendrimers have remarkable molecular monodispersity and suitable pharmacokinetic properties for systemic drug delivery with cleavable chemistry for drug dissociation . Amphiphilic dendrimers are able to form micelles by self-assembly with hydrophilic groups on the surface for functionalization. Drug release kinetics

are controlled through the properties of the polymer chains, which can be designed to be degraded for release of a payload. Baker et al. have developed “avidimers”, which are dendrimers targeted to tumor vasculature using a methotrexate polyamidoamine(PAMAM) bioconjugate platform functionalized with small targeting ligands. Non-targeted and folate-targeted G5-PAMAM dendrimers differentially accumulated into a human KB cell line xenograft tumor model within a day (8%–10% targeted versus 2% non-targeted I.D./g of tissues). Higher accumulation in the tumor resulted in the inhibition of tumor growth, lower toxicity, and longer survival time compared to free drug at equal dosage. More importantly, recent efficacy studies using targeted transferrin-cyclodextrin-siRNA nanoparticles (CALAA-01, ~70 nm) in animal models of human epithelial cancer showed tumor size reduction and differential distribution in tumors. The preclinical data motivated further development of CALAA-01. The toxicological results reported in April 2007 for CALAA-01, which was the first targeted, polymeric nanoparticle platform in non-human primates, led to the submission of an investigational new drug application and human clinical trials for solid tumor therapy in May 2008.

6. Polymersome Nanoparticles

Polymersomes have a structure similar to liposomes, but are composed of synthetic polymer/polypeptide amphiphilic and self-assemble to form polymer shell vesicles (~100 nm) when hydrated and extruded. Discher et al. described vesicles made of amphiphilic diblock copolymers with low water permeability. The hydrophilicity/hydrophobicity ratio is used to control the morphology of the nanoparticle, which can range from spherical to cylindrical. The membrane core thickness can be controlled by the molecular weight of the diblock copolymer. Polymersomes show higher stability and lateral fluidity than liposomes and the release is triggered by the degradation of the polymer chain and destabilization of the shell layer. Incubation of polymersomes in the blood showed adherence and uptake by white blood cells within 10 h. In vivo results using a breast cancer tumor xenograft model showed therapeutic efficacy after a single i.v. injection using polymersomes loaded with paclitaxel and doxorubicin at the maximum tolerated dose (2.5 mg/kg for each drug).

7. Protein Nanoparticles

Protein-based drug delivery systems have recently made a big impact with albumin bound drug nanoparticles (~130 nm). The recent approval of albumin-bound paclitaxel by the Food and Drug Administration (FDA) for metastatic breast cancer therapy, as well as multiple clinical trials currently in progress for other types of cancer, has now opened the possibility of using protein-based nanoparticles for delivery of therapeutic agents. Given the limiting pharmacokinetic

properties and numerous side effects of Taxol (hypersensitivity), the albumin-bound paclitaxel allows the formulation of the hydrophobic drug in a solvent-free solution. Albumin is a natural noncovalent physiological transporter of molecules across endothelial barriers through transcytosis-mediated mechanism (caveolae vesicle). Preclinical studies have shown that the concentration of paclitaxel bound to albumin in endothelial cells and in the extravascular space was significantly increased (3–10 fold). Data suggests that albumin may have intrinsic targeting abilities to tumors, although the enhanced permeability and retention (EPR) effect may play an additional role in tumor accumulation. Overall, the albumin-bound paclitaxel formulation allowed higher dosages than the Taxol formulation (260 mg m⁻² vs. 175 mg m⁻², respectively) and demonstrated improved efficacy and safety. Abraxane is currently being tested as a first-line therapy or in combination with other drugs (rapamycin, verinostat, etc.) for metastatic breast cancer and other cancers that have been shown to be sensitive to taxane drugs, such as ovarian and prostate. In addition, albumin is now being tested as a platform for delivery of other molecules that have reduced water solubility, such as rapamycin (~2.5 mg ml⁻¹). Albumin-bound rapamycin (ABI-009) has been in a clinical phase trial for the treatment.

8. Biological Nanoparticles

Biological nanoparticles such as bacteria are unicellular microorganisms with different shapes and sizes that encapsulate essential components of the cytoplasm as well as hydrophobic and hydrophilic molecules. One example of biological nanoparticles being evaluated for cancer therapy is a drug delivery system developed by EnGeneIC Pty Ltd called a “nanocell”, which consists of anucleate globular bacteria (~400 nm). The absence of DNA prevents endogenous mutations and replication originally reported in 1967. It has been demonstrated that a nanocell can be efficiently loaded with molecules of different solubility and charge, such as doxorubicin, paclitaxel, and siRNA, through drug diffusion into the bacteria within a few hours. No signs of toxicity have been reported in large animals such as pigs and monkeys with repeated dosages at high titers, although there is the potential.

9. Inorganic Nanoparticles

Inorganic nanoparticles are primarily metal-based and have the potential to be synthesized with near monodispersity. Inorganic materials have been extensively studied for imaging using magnetic resonance and high-resolution superconducting quantum interference devices while their intrinsic properties have been explored for therapy. Several types of metal nanoparticles are able to convert energy into heat at levels up to 70°C through near-infrared light excitation or oscillating magnetic field stimulation. Iron oxide nanoparticles coated with aminosilane (Nanotherm M01) are

in clinical phase II trials in Germany for brain cancer therapy and recurrent prostate cancer therapy using hyperthermia as well as thermo ablation methods. The phase I results showed that prostate tumor cells can be locally killed by magnetic iron oxide nanoparticles .

Nanoparticles were injected locally using ultrasound to guide tumor injections and patients were treated once a week for 1 h over two months. The small nanoparticles (~20 nm) are able to penetrate tumors, enter cancer cells, and generate heat under magnetic fields(50 and 100 kHz), allowing treatment width between 20 and 30 cm and within acircular area of 20 cm of diameter. The authors report no dose-limiting toxicities and mild discomfort from internal heating. Similarly, silica nanoparticles coated with gold that absorb near-infrared laser energy and covert it into heat to kill solid tumors are currently under investigation in a pilot study for head and neck cancer therapy. In vivo results of nanoshell-mediated NIR (near infrared) thermal therapy using human breast cancer xenograft models showed that the nanoparticles induced irreversible cancer tissue damage at a temperature~40_C. However, the temperature variance between different mice treated was quite significant (28–60_C) and was suggested to be due to differential distribution of nanoshells in the treated volume of the tumor. In addition, the maximum recorded temperature was only ~1 mm under the skin. Recently, the same nanoparticles(150 nm) were used for brain cancer treatment in an orthotopic canine model .

Tumors were killed using percutaneous in filtrated NIR fibers reaching a temperature of ~70_C in tumor tissues and ~50_C in normal white and grey matter, which is expected to significantly damage non-diseased areas of the brain. Surface properties and functionalities of gold nanoparticles have also been used for the delivery of surface-bound therapeutics. Aurimune (CYT-6091) is an example of tumor necrosis factor (TNF)-alpha bound to PEG-coated gold nanoparticles(~27 nm) developed by CyImmune Sciences, Inc. for solid tumorthrapy . TNF-alpha is a potent cytokine with antitumor cytotoxicity which requires incorporation into a nanocarrier formulation to reduce systemic toxicity. The results show that nanoparticle formulations delayed the tumor growth with local heating (42_C for 1 h) using a SCK mammary tumor xenograft mouse model. However, the combined treatment showed a higher efficacy and suppression of intratumor blood flow .

Preliminaries micrographs of nanoparticles accumulated in breast tumor tissue sections in contrast to healthy tissues showed possible targeting of the nanoparticles by the EPR effect. Many other formulations are still in the discovery stage using combinations of drugs such as TNF with paclitaxel, doxorubicin or interleukin-12.However, the load of therapeutic agent is reported to be several hundreds of molecules due to the surface adsorption density, which may limit the effect of

he therapeutic agent. Recently, Adair's group has reported the encapsulation of organic molecules in calcium phosphate Nano composite particles (~27 nm) for intracellular imaging and delivery. Calcium phosphate-based nanoparticles are biocompatible and their pH dissolution properties can be used for controlled release of molecules in the acidic tumor environment. In vitro studies show high uptake of the nanoparticles in bovine aortic endothelial cells and the delivery of hexanoyl-ceramide (Cer-6) to human vascular smooth muscle cells showed 100% inhibition of cell growth at 200 nM of drug.

This technology is now being developed by Keystone Nano for imaging and delivery of therapeutic agents. On-specific accumulation into healthy tissues is always a concern for nanoparticle drug delivery systems. Using local sensitization through light or temperature may reduce overall toxicity, but it is expected to damage adjacent healthy tissues as well. Ultimately, inorganic particles may not provide advantages over other types of nanoparticles for systemic targeting of cancer cells because they are not biodegradable.

10. Hybrid Nanoparticles

Hybrid nanoparticles are recently developed nanocarrier that combine advantages from existing systems with well-characterized properties to form lipid-polymer nanoparticles and solid liposomal nanoparticles. Hybrid nanoparticles are composed of at least two different materials to form the core and the corona structure. In general, metallic and polymeric materials form the core and are coated with a single or multiple lipid layers to form a protecting membrane (corona) similar to a liposome or micelle. We and others have developed hybrid nanoparticles for cancer therapy. Sasisekharan and co-workers have reported PLGA-core nanoparticles coated with a bi-phospholipid layer to carry multiple drugs for cancer therapy using melanoma and Lewis lung carcinoma models. In their system, doxorubicin is conjugated to PLGA to form the core of the nanoparticle (~1% load by weight of doxorubicin, 70% encapsulation efficiency) while an anti-angiogenesis drug, combrestatin, is mixed with phospholipids and encapsulated in the lipid bi-layer during the self-assembly process to form nanoparticles (~200 nm) described as "nanocells". The drugs were release at different rates over a period of ~3 days, with combrestatin released first to reduce vascular density in the tumor followed by the release of doxorubicinto kill the cancer cells. The results showed a significant delay in tumor growth and increased survival time in both cancer models, suggesting accumulation of then anocell by the EPR effect and added therapeutic value by delivering multiple drugs.

The nanocell technology is now in preclinical development by Cerulean Pharma. Others have reported solid-lipid nanoparticles using different polymers and formulations in vitro and in vivo for

combination therapy. Recently, Thevenot *et al.* described a mechanism for the encapsulation of a hydrophobic polymer core (PLA) in PEG-liposomes. As part of the work, the importance of PEG chain length to sterically stabilize lipoparticles with optimal colloidal stability was demonstrated (PEG (5 kDa) at 10% of lipid content). Our group has reported a one-step formulation for self-assembly of a single layer of lipid on the hydrophobic surface of PLA nanoparticles (size <100 nm).

Surface functionalization using different lipid constituents allows the precise control of the charge and targeting ligand density, leading to stable hybrid nanoparticle formulations. In addition, drug loading was significantly increased up to ~8% by weight and the release kinetics of docetaxel was shown to be controlled by the lipid layer on the surface of the nanoparticles. Multifunctional nanoparticle technologies are now able to combine multiple therapeutic approaches that approaches such as photothermal and drug delivery, and simultaneous delivery of therapeutic drugs and imaging agents.

Statistics for Cancer Therapy Using Nanoparticles^{5,6,7}

1. Metastatic Cancer

Metastatic cancer is a clinical description for the spread of cancer cells from the primary tumor site to distant organs, establishing secondary tumor sites. Detachment of cancer cells from the primary tumor site and circulation in the blood allows the cells to arrest in organs such as the lungs, liver, lymph nodes, skin, kidneys, brain, colon, and bones, where they can extravasate and proliferate. Despite significant increases in the understanding of metastatic cancer pathogenesis, early diagnosis, surgical methods, and irradiation treatment, most cancer deaths are due to metastases that are not curable. Reasons for this include resistance to treatments, difficulty accessing the tumor sites and removing all cancer cells during surgery, or physiological barriers for drug access such as the blood-brain barrier (BBB). Therefore, improving therapy of metastatic cancer is still a challenge even though multiple therapeutic approaches are approved or in clinical development. An improved understanding of cancer biology, including microenvironment functions, signalling pathways, and metastasis evolution, has resulted in clear advances in cancer therapy. Drugs have now been developed against a range of targets including matrix metalloproteinase inhibitors, epidermal growth-factor receptor inhibitors, transferase inhibitors, migration inhibitors, and angiogenesis inhibitors. However, due to the complexity of tumor progression, tumor composition blood vessel structures, and drug resistance mechanisms, most of the current therapies have provided limited extension of

survival time across multiple cancer types with the exception of imatinib (tyrosine kinase inhibitor) for gastrointestinal stromal tumor .

Knowledge of drug action pathways and cellular drug resistance mechanisms to specific drugs has allowed the development and evaluation of promising drug combinations . Trials of combinations of agents are usually designed to enhance the activity of the primary agent or to inhibit different pathways to circumvent drug resistance to the primary agent. The critical advantage of using drug combinations is to prevent drug resistance development during cancer therapy without increasing the known side effects of each drug. Although it is believed that tumor growth and metastases are adaptable mechanisms, higher doses of single drugs are able to prevent resistance mechanisms in vitro in some cases . However, multi-drug regimens with synergistic combinations have been shown to be more successful in patients, probably due to cell heterogeneity in tumors and between patients. Unfortunately, multi-drug treatment requires complicated dosing regimens. Nanoparticle delivery systems offer solutions to both of these approaches. Delivery of single drugs in nanoparticles results in increased drug concentrations in the tumor, allowing higher doses compared with free drug using both non-targeted and targeted delivery. Nanoparticles can also be engineered to carry multiple drugs that are delivered together in one particle with control over the release rate of each drug, preventing the need for complicated multi-drug dosing regimens and improving patient compliance.

2. Non-Targeted Nanoparticles

Non-targeted nanoparticles circulating in the blood have been shown to significantly improve drug bioavailability and accumulation in tumors through the enhanced permeability and retention effect (EPR) . The EPR effect allows the passive targeting of nanoparticles to tumors due to pathological abnormalities in the tumor vasculature . Interendothelial gap defects increase vascular permeability in tumors, allowing extravasation of nanoparticles up to 400 nm . Accumulation of nanoparticles is further enhanced due to poor lymphatic drainage in tumors. The local release of anti-cancer drugs from nanocarriers in the extravascular space results in an increased intra-tumoral drug concentration. In general, hydrophobic drugs released extracellular will diffuse and be taken up by cancer cells, leading to enhanced tumor cytotoxicity. Since cancer cell populations, cell density, antigen expression, microenvironment, and vasculature density are significantly different across different cancers and even within primary and secondary metastatic sites, nanoparticle biodistribution and circulation time represent critical parameters for cancer therapy.

Multiple factors affect the pharmacokinetic behavior of nanoparticles, but the surface charge, size, nanoparticle shape and stealth properties are among the most critical . As described in the

nanoparticle technologies section above, five common types of nanoparticles are approved or in late stage of clinical trials, including polymer–drug conjugates, micelles, protein-based carrier, liposomes, and polymeric nanoparticles. Overall, non-targeted nanoparticles accumulate in tumor xenograft mice models in the range of 1–4% of I.D./g of tissue, although these numbers are difficult to compare due to different post-injection time assessments . Polymer–drug conjugates are the smallest (1–20 nm) and have a circulation half-life in human ranging from hours to days depending on the system. To our knowledge, dextran–camptothecin (DE-310) has the longest circulation half-life (~300 h) in humans and has been shown to have no major toxicity compared to the free drug formulation in clinical phase II trials . However, its therapeutic efficacy might be limited by its dosage regimen compared to PEG–camptothecin and polyglutamate–camptothecin conjugate. (7,000 and 25 mg m₂, respectively) .

These results underline the significant differences of pharmacokinetic parameters using different polymer–drug conjugates due to different loading, release profiles, and molecular weights of the carrier. This is also true for the circulation half-life of other Multiple factors affect the pharmacokinetic behavior of nanoparticles, but the surface charge, size, nanoparticle shape and stealth properties are among the most critical . As described in the nanoparticle technologies section above, five common types of nanoparticles are approved or in late stage of clinical trials, including polymer–drug conjugates, micelles, protein-based carrier, liposomes, and polymeric nanoparticles. Overall, on-targeted nanoparticles accumulate in tumor xenograft mice models in the range of 1–4% of I.D./g of tissue, although these numbers are difficult to compare due to different post-injection time assessments . Polymer–drug conjugates are the smallest (1–20 nm) and have a circulation half-life in human ranging from hours to days depending on the system. To our knowledge, dextran–camptothecin (DE-310) has the longest circulation half-life (~300 h) in humans and has been shown to have no major toxicity compared to the free drug formulation in clinical phase II trials. However, its therapeutic efficacy might be limited by its dosage regimen compared to PEG–camptothecin and polyglutamate–camptothecin conjugates(7,000 and 25 mg m₂, respectively) . These results underline the significant differences of pharmacokinetic parameters using different polymer–drug conjugates due to different loading, release profiles, and molecular weights of the carrier. This is also true for the circulation half-life of others. Polymer–drug conjugates such as HPMA–drug conjugates, polyglutamate–drug conjugates, dextran–drug conjugates and pegylated drugs such as PEG–argininede aminase (Hepacid, 7 days) and PEG–camptothecin (Prothecan, 40 h) . In general, larger nanoparticles such as micelle sand liposomes seem to have a shorter circulation half-life in the blood (2–50 h) but higher maximum tolerated

doses. The Genexol-PM formulation of paclitaxel is given at a twofold higher dosage than HPMA-paclitaxel (PNU166945) and polyglutamate - paclitaxel (Xyotax). However, it is not clear whether circulation half life or maximum tolerated dose is the most critical for optimum accumulation in tumor tissues. For example, polycyclodextrin-camptothecin micelles (IT-101) and PEG-camptothecin conjugates show similar circulation half-life but significantly different accumulation of drug in tumor xenograft models. However, this may be due to the different xenograft models used. Unfortunately, it is difficult to compare the therapeutic efficacy of different systems in humans due to different patient populations and disease stages.

Clinical data suggests that the circulation half-life and biodistribution of nanoparticles are related to the physicochemical properties of the vehicle. This is consistent with the *in vivo* biodistribution and circulation half-life results using animal models. In addition, it is well established that hydrophilic polymers such as PEG can be grafted, conjugated, or absorbed onto the surface of nanoparticles to form a corona, which provides steric stabilization and confers “stealth” properties by reducing protein adsorption and rapid clearance. Recently, we and others ; investigated nanoparticle surface properties and adsorption of proteins present in the blood. Lindman et al. found that protein adsorption kinetics and composition depends on particle size and surface hydrophobicity. The results show that albumin adsorbed more on the surface of 200 nm nanoparticles than on smaller nanoparticles (70 nm). Nanoparticles with hydrophilic surfaces significantly prevented protein adsorption. It was suggested that smaller nanoparticles (70nm) have higher curvature which reduce protein adsorption of larger proteins. Interestingly, the results show a binding competition leading to adsorption exchanges between proteins despite different concentrations and affinities. Lundqvist et al. have shown that protein adsorption depends significantly on the size and charge of the nanoparticles. Identification of protein compositions bound to the nanoparticles showed a mixture of proteins with different functions such as immunoglobulin, lipoproteins, complement pathways proteins, and coagulation factor proteins. Similarly, our group investigated complement activation, blood clotting, and protein adsorption properties

of hybrid nanoparticles with precise control of the charge .DeSimone’s group has investigated internalization pathways and *in-vivo* biodistribution of polymeric nanoparticles with different size and shapes . Nanoparticles were more efficiently taken up by Hela cells than microparticles. Rod-like nanoparticles were internalized efficiently than their spherical counterpart *in vitro* but there was no clear evidence of the effect of shape affecting the biodistribution and circulation half-life of the nanoparticles *in vivo*. Other groups have also shown differential uptake of nanoparticles with

different shapes . These findings are highlighted by the mechanical modeling reported by Decuzzi showing that nanoparticle geometry and physicochemical properties contribute to the cellular internalization rate and adhesion forces on the surface of the cells. Mathematical models suggest that nanoparticle size will control its interaction with cells, especially the endothelial wall of vasculatures through a margination dynamic mechanism. Finally, the surface structure of the nanoparticle can affect its cellular uptake. Recent studies have shown that nanoparticles coated with sub-nanometer striations demonstrate enhanced uptake compared with random.

3. Targeted Nanoparticles

The concept of targeted therapy appeared in the late 1970s with the development of antibodies , whereas the application of targeted nanoparticles appeared later using immune liposomes .Advances in cancer proteomics and bioinformatics have allowed the development of targeted therapies, which were referred to as a “magic bullet” by the visionary Paul Ehrlich . Nano carriers may be surface functionalized with biomolecules for “active” tumor targeting. Surface ligands include antibodies, aptamers, peptides, or small molecules which recognize tumor-specific or tumor-associated antigens in the tumor microenvironment . The active targeting mechanism takes advantage of highly specific interactions between the targeting ligand and certain tissues or cell surface antigens to increase cellular uptake and increase tumor retention. Conjugation approaches have been developed to control the amount of targeting ligands on the surface of the nanoparticles. In the case of weak binding ligands, multivalent functionalization on the surface of the nanoparticles provides sufficient avidity. In general, small molecule ligands such as peptides, sugars, and small molecules are more attractive than antibodies due to higher stability, higher purity, ease of production through synthetic routes, and non-immunogenicity.

There are two common approaches for receptor-mediated targeting. This first approach is to target the tumor microenvironment, including the extracellular matrix or surface receptors on tumor blood vessel endothelial cells, which is usually most efficient for the delivery of immune induction or antiangiogenesis molecules. The second approach is to target tumor cell surface receptors for intracellular delivery of cytotoxic agents or signal-pathway inhibitors. Nanocarriers targeted to the extracellular portion of transmembrane tumor antigens are generally specifically taken up by cancer cells through receptor-mediated endocytosis for efficient delivery of therapeutic loads intracellularly.

Although it is not clear which approach will provide the highest therapeutic efficacy for treatment of cancer metastases, a recent report using integrin receptor targeted nanoparticles delivering a cytotoxic drug (doxorubicin) showed promising data in primary and metastatic sites of human

renal and pancreatic carcinoma mouse xenograft models . Targeted nanoparticles showed tumor accumulation and decreased the tumor weight in the primary tumor and hepatic lymph node metastasis. We and others have developed targeted nanoparticles for multiple cancer types.

Our group has developed nucleic acid aptamer functionalized nanoparticles for controlled drug delivery. Aptamers are able to bind to specific targets with high affinity and specificity, resulting in clinical development for multiple applications .We are developing multiple technologies using targeted nanoparticle–aptamer bioconjugates for drug delivery to prostate cancer. In a proof-of-concept study, polymeric nanoparticles utilizing aptamers as the targeting ligand showed almost complete reduction in tumor growth in a human prostate cancer tumor xenograft mice model . All the treated mice survived more than three months in contrast to other controls. Subsequently, we reported a novel strategy for formulating targeted nanoparticles that was tested in vivo . We also engineered hydrophilic cisplatin drugs for efficient encapsulation into PLGA–PEG nanoparticles.

Plasmonic Photothermal Therapy Using Gold Nanoparticles^{8,9}

The use of heat has become one of the major methods for tumor therapy since its ancient usage in 1700 BC when a glowing tip of a fired rill was used for breast cancer therapy . Later heating sources ranging from radio frequency to microwaves as well as ultrasound waves were introduced to induce moderate heating in a specific target region, which is termed as hyperthermia. Hyperthermia is commonly defined as heating tissue to a temperature in the range 41–47°C for tens of minutes. Tumors are selectively destroyed in this temperature range because of their reduced heat tolerance compared to normal tissue, which is due to their poor blood supply. Hyperthermia causes irreversible cell damage by loosening cell membranes and denaturing proteins. But the applications of the heating sources conventionally employed for hyperthermia are limited because of their damage to surrounding healthy tissues.

A revolution in cancer therapy has taken place by the emerging use of laser light to achieve controlled and confined thermal damage in the tumor tissue. Laser, the acronym for light amplification by the stimulated emission of radiation , is an optical source that emits photons in a coherent and narrow beam. It was proposed in 1959 and first demonstrated in 1960 . Laser usage in surgery was first reported by ophthalmologists in 1963 and then reported for tumor eradication in 1965 followed by wide interest in late 1960s . The laser light, usually neodymium–yttrium aluminium garnet (Nd–YAG, 1.06 μm) and CO₂ laser (10.6 μm) can either be transmitted from optical fiber tip to exposed tumors in the air or delivered into a confined space by inserting the bare end of the fiber into the centre of the target tumor, which is often called interstitial laser hyperthermia . Laser light has the characteristics of monochromaticity, coherence, and collimation

. These properties provide an arrow beam of high intensity, which transmits deep down into the target tissue with minimal power loss and great precision.

The biggest disadvantage of laser therapy is its no selectivity. Both normal and tumor cells in the path of the laser light are damaged. The requirement of the high power density is another problem. High power laser output up to tens to hundreds of watts has to be used to efficiently induce the tumor ablation. Another type of tumor therapy method is the photodynamictherapy (PDT), also known as photo chemotherapy, which involves cell destruction caused by means of toxic singlet oxygen and/or other free radicals that are produced from a sequence of photochemical and photobiological processes. These processes are initiated by the reaction of a photosensitizer with tissue oxygen upon exposure to a specific wavelength of light in the visible or near-infrared (NIR) region. The earliest sensitizer used was acridine, which was reported in 1900 to kill paramecia and followed by eosin for skin cancer treatment in 1903.

Although many chemicals have been later reported for photochemical therapy, porphyrin-based sensitizers lead the role in clinical applications because of their preferential retention in cancer tissues and due to the high quantum yields of singlet oxygen produced. The Photofrin, which is a purified hematoporphyrin derivative, has been approved for clinic trials by the US Food and Drug Administration. Porphyrin-based therapy can only be used for tumors on or just under the skin or on the lining of internal organs or cavities because it absorbs light shorter than 640 nm in wavelength. For deep-seated tumors, second generation sensitizers, which have absorbance in the NIR region, such as core-modified porphyrins, chlorins, phthalocyanine, and naphthalocyanine have been introduced. A major drawback of PDT is that the photosensitizing drug stays in the body for a long time, rendering the patient to be highly sensitive to light.

An alternative to PDT is the photothermal therapy (PTT) in which photothermal agents are employed to achieve the selective heating of the local environment. When the PTT agents absorb light, electrons make transitions from the ground state to the excited state. The electronic excitation energy subsequently relaxes through nonradioactive decay channels. This results in the increase in the kinetic energy leading to the overheating of the local environment around the light absorbing species. The heat produced can be employed for local cell or tissue destruction. The photoabsorbing agents can be natural chromophores in the tissue or externally added dye molecules such as indocyanine green, naphthalocyanines, and porphyrins coordinated with transition metals. Natural chromophores, however, suffer from very low absorption. The choice of the exogenous photo thermal agents is made on the basis of their strong absorption cross sections and highly efficient light-to-heat conversion.

This greatly reduces the amount of laser energy required to achieve the local damage of the diseased cells, rendering the therapy method less invasive. But the problem with dye molecules is their photo bleaching under laser irradiation. In recent years, the tremendous development of nano technology has provided a variety of nanostructures with unique optical properties that are useful in biology and biomedical applications . From the point of the view of cancer therapeutics, noble metal nanoparticles become very useful as agents for PTT on account of their enhanced absorption cross sections, which are four to five orders of magnitude larger than those offered by conventional photo absorbing dyes. This strong absorption ensures effective laser therapy at relatively lower energies rendering the therapy method minimally invasive. Additionally, metal nanostructures have higher photostability, and they do not suffer from photo bleaching. Currently, gold nanospheres, gold nanorods , gold nanoshells, gold nanocages , and carbon nanotubes are the chief nanostructures that have been demonstrated in photothermal therapeutics due to their strongly enhanced absorption in the visible and NIR regions on account of their surface plasmon resonance (SPR) oscillations. Of these structures, the first three nanostructures are especially promising because of their ease of preparation, ready multi-functionalization, and tunable optical properties. In the present review, we discuss the photothermal properties of these plasmonic nanostructures and their application in selective PTT. We propose the name plasmonic photothermal therapy (PPTT) for this treatment to distinguish it from PTT and PDT.

Photothermal properties of plasmonic goldnanoparticles^{10,11,12}

In 1857, Faraday made colloidal gold for the first time by reducing gold chloride with phosphors and recognized that the reddish color was due to the small size of the colloidal gold particles. In 1951, Turkevich et al. simplified the method by using sodium citrate as reducing agents. Since then, the interaction between light and gold nanoparticles has been widely studied .Gold nanoparticles absorb light strongly in the visible region due to the coherent oscillations of the metal conduction band electrons in strong resonance with visible frequencies of light. This phenomenon is known as the SPR. The SPR frequency is dependent on the type of the metal, the size and shape of the metal nanoparticles, as well as the dielectric constant of the surrounding medium, thus imparting a unique optical tunability to the nanostructures. When the size increases, the surface Plasmon absorption maximum slightly redshifts .

When the nanoparticles form assemblies or aggregates, the surface plasmon absorption maximum redshifts to the NIR region. Interestingly, when the shape of the gold nanoparticles is changed from sphere to rod, the SPR spectrum splits into two bands: a stronger long-wavelength band in the NIR region due to the longitudinal oscillation of electrons and a weaker short-wavelength band in

the visible region around 520 nm due to the transverse electronic oscillation. Unlike spherical nanoparticles, the absorption spectrum of the gold nanorods is very sensitive to the aspect ratio (length/width). With an increase in the nanorod aspect ratio, the SPR absorption wavelength maximum of the longitudinal band significantly redshifts. Similarly, when the solid gold nanospheres are changed to gold shell structures, the absorption maximum also greatly redshifts. In 1998, Halas and coworkers at Rice University developed the gold nanoshell structure, which is composed of a silica core (100–200 nm in diameter) surrounded by a thin layer of gold shells (5–20 nm). Then nanoshells absorb and scatter strongly in the NIR region. The optical resonance of the nanoshells can be tuned by adjusting the ratio of the thickness of the gold shell to the diameter of the silica core. It has been shown that the smaller this ratio, the more red shifted is the SPR wavelength.

The photothermal properties of gold nanoparticles have been systematically studied using femtosecond transient absorption spectroscopy by Link and El-Sayed, who have shown that the photo excitation of metal nanostructures results in the formation of a heated electron gas.

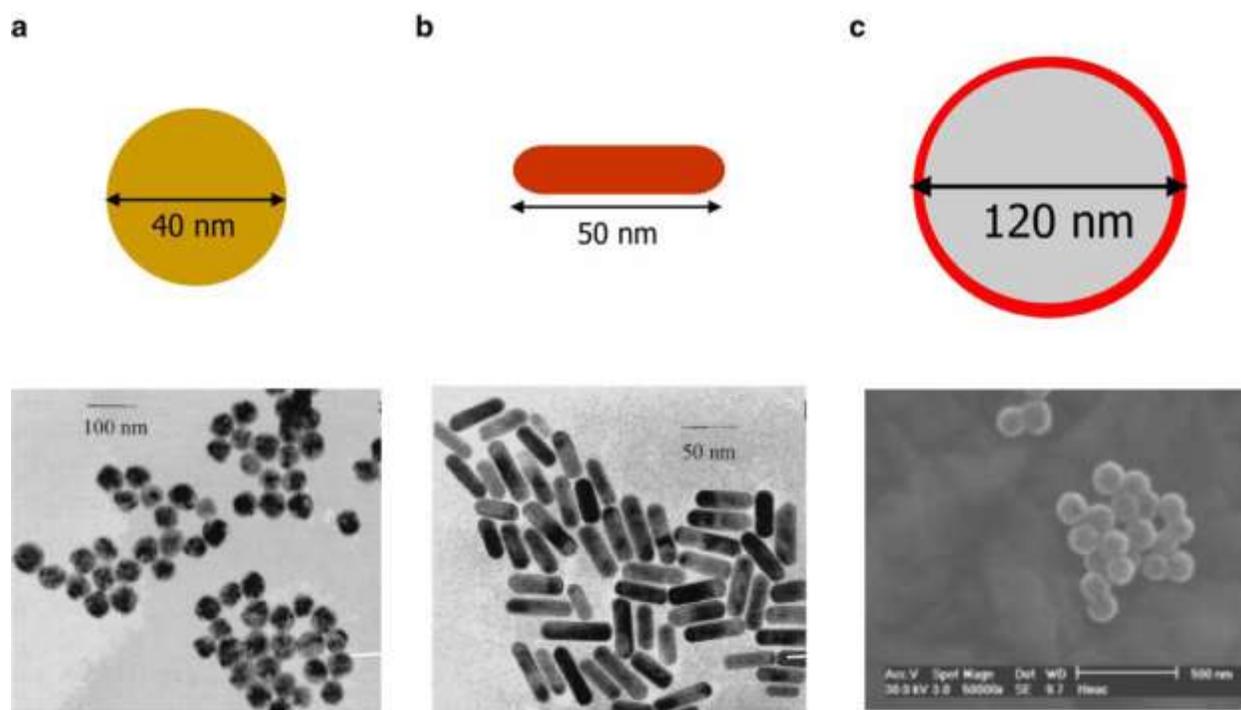


Figure 3: Plasmonic gold nanostructures commonly used for PPTT.

a Nanospheres (transmission electron microscopy [TEM] image reproduced with permission from [1]); **b** nanorods (TEM image reproduced with permission from [2]); **c** Nanoshells (TEM image reproduced with permission from [3]).

Photothermal properties of plasmonic gold nanoparticles

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The nanoshells absorb and scatter strongly in the NIR region. The optical resonance of the nanoshells can be tuned by adjusting the ratio of the thickness of the gold shell to the diameter of the silica core. It has been shown that the smaller this ratio, the more redshifted is the SPR wavelength. The photo thermal properties of gold nanoparticles have been systematically studied using femtosecond transient absorption spectroscopy by Link and El-Sayed, who have shown that the photoexcitation of metal nanostructures results in the formation of a heated electron gas that subsequently cools rapidly within ~ 1 ps by exchanging energy with the nanoparticle lattice. This is followed by phonon–phonon interactions where the nanoparticle lattice cools rapidly by exchanging energy with the surrounding medium on the timescale of ~ 100 ps. This fast energy conversion and dissipation can be readily used for the heating of the local environment by using light radiation with a frequency strongly overlapping with the nanoparticle SPR absorption band.

The intense SPR-enhanced absorption of gold nanoparticles makes the photothermal conversion process highly efficient. The absorption cross section of gold nanoparticles of magnitude stronger than the strongest absorbing Rhodamine6G dye molecules. Hot electron temperatures of several thousand kelvins are easily reached in the nanoparticles even with laser excitation powers as low as 100 mW and the lattice temperature on the order of a few tens of degrees can be achieved.

This highly efficient production of heat energy from the absorbed light energy by gold nanoparticles make them greatly promising in the PPTT of cancers and other diseases. Further, in the case of gold nanorods and gold nanoshells, this strong absorption can be tuned to the NIR region a region where light penetration is optimal due to minimal absorption from tissue chromophores and water. This makes NIR-resonant gold nanostructures very useful for clinical therapy applications involving tumors located deep within bodily tissue. In addition to the local heating of the surrounding environment, which leads to irreversible cell destruction through protein denaturation and coagulation as well as cell membrane destruction, bubble formation around gold nanoparticles is also involved in the case of short pulse laser irradiation, which imposes mechanical stress leading to cell damage. Irradiation with short laser pulses has been shown to lead to the rapid heating of the particles and vaporization of a thin layer of fluid surrounding each particle, producing a microscopic version of underwater explosion and cavitation bubble formation Zharov *et al.* also found that nanoclusters formed by the assembly of gold nanoparticles on human breast cancer cells significantly enhance the bubble formation causing more efficient cancer cell killing. Very recently Khlebtsov *et al.* theoretically simulated the photothermal conversion efficiency of the different nanostructures including gold nanospheres, gold nanorods, gold nanoshells, linear chains, 2D arrays, and 3D clusters by calculating their SPR absorption spectra.

It was found that gold spheres with diameters of about 30–40 nm are most preferable, as their normalized absorption is maximal in the visible spectrum region. The nanorods with length between 15 and 70 nm were predicted to be most efficient. Of course, it would also be required that the longitudinal absorption maximum be matched to the wavelength of the NIR laser to get optimal photothermal efficiency. Goldnanoshells with external diameters of about 50–100 nm and gold shell thicknesses of about 4–8 nm are estimated to be the most effective due to the strong absorption and low scattering near 800 nm. Bioconjugation and targeting Most laser-based therapeutic methods rely on the use of endoscopes and fiber optic catheters to deliver light specifically to the tumor region.

Plasmonic gold nanostructures thus show great promise for the selective PTT for cancer as well as other diseases. We propose the name PPTT for this treatment. It is realized that a number of variables need to be further addressed, e.g., stability, biocompatibility, and chemical reactions of nanoparticle bioconjugates in physiological environments, blood retention time, tumor extravasation, the fate of the nanoparticles following therapy, etc. We anticipate that the success and promise of the initial use of plasmonic nanoparticles for selective PPTT could be efficiently extended to clinical stage once the optimal parameters of these variables are identified, as is being done through current research studies.

Gold Nanoparticles And Synthesis^{13,14,15}

Generally, gold nanoparticles are produced in a liquid ("liquid chemical methods") by reduction of chloroauric acid ($\text{H}[\text{AuCl}_4]$), although more advanced and precise methods do exist. After dissolving $\text{H}[\text{AuCl}_4]$, the solution is rapidly stirred while a reducing agent is added. This causes Au^{3+} ions to be reduced to neutral gold atoms. As more and more of these gold atoms form, the solution becomes supersaturated, and gold gradually starts to precipitate in the form of sub nanometer particles. The rest of the gold atoms that form stick to the existing particles, and, if the solution is stirred vigorously enough, the particles will be fairly uniform in size. To prevent the particles from aggregating, some sort of stabilizing agent that sticks to the nanoparticle surface is usually added. They can be functionalized with various organic ligands to create organic inorganic hybrids with advanced functionality. It can also be synthesised by laser ablation



Figure 4 Steps of Gold Nanoparticles Synthesis

Shapes

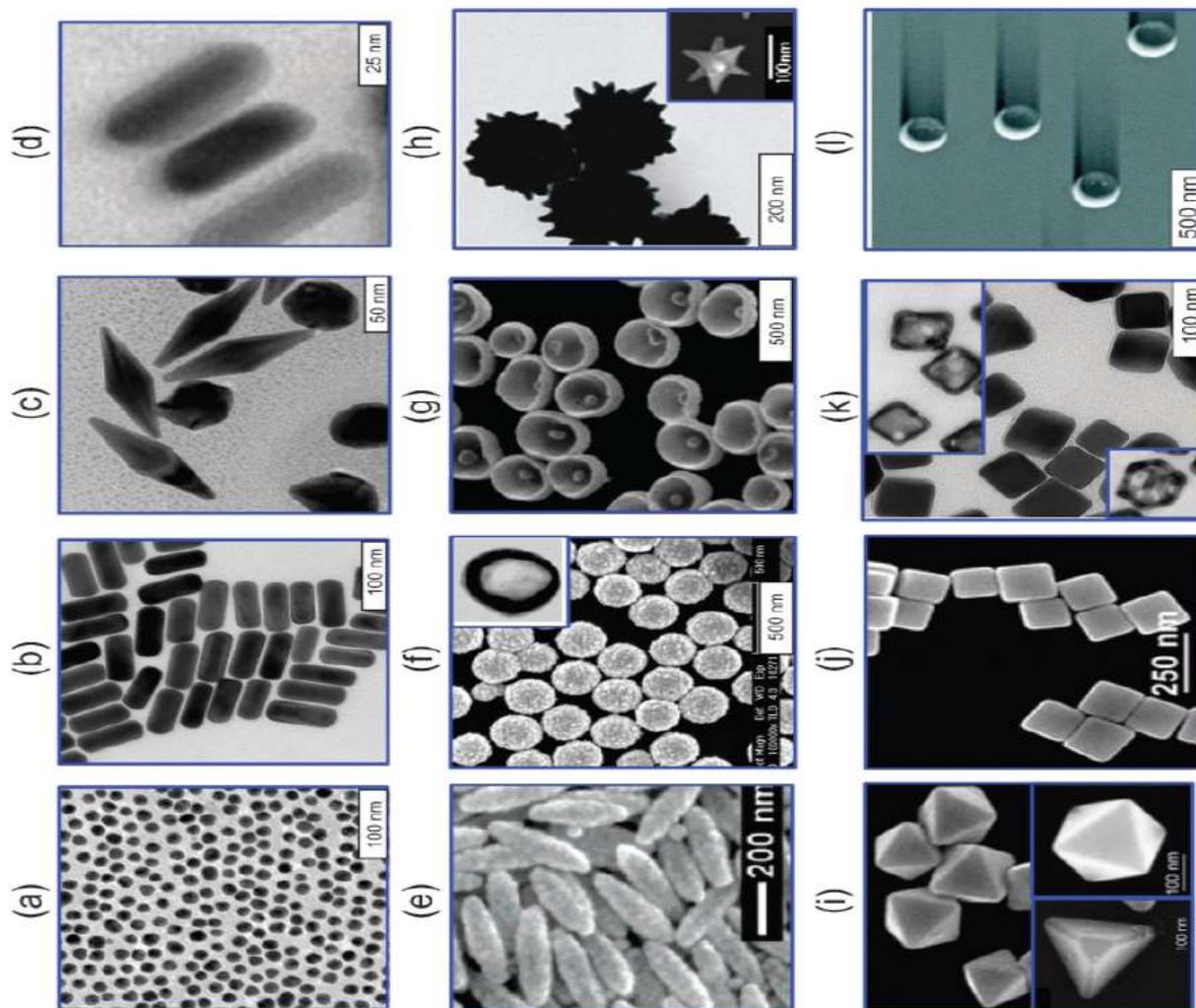


Figure.-5 Various types of nano particles

Synthesis of various gold nanoparticles^{16,17}

Gold nanorods

In gold nanorods, electrons can oscillate in two independent directions (along the main axes and perpendicular to it): this generates two SPR absorption bands, the first one (perpendicular) being at the typical nanoparticles wavelengths and the second (longitudinal) in the NIR region. Gold nanorods, which were developed during the same period as gold-silica nanoshells, are generally smaller than nanoshells. Like gold-silica nanoparticles, gold nanorods fluence threshold for gold nanorod conversion, photothermal therapy would still be effective for tumors within 10 mm of the illuminated region. This correlates with the limitations in vivo of NIR laser penetration.

Gold nano shells

In 2003, Hirsch *et al.* were the first to demonstrate photothermal therapy using gold-silica nanoshells. Gold-silica Nano shells, composed of silica cores with a thin overlay of gold, were the

first gold nanoparticles easily tunable to the NIR. By varying the size of the silica core and the thickness of the goldshell, the resonance of these nanoshells can span from the visible to the near infrared. Gold–silica nanoshell fabrication is based on seed-mediated growth, where ‘seeds’ of gold colloid are attached to the silica cores, and additional gold is added for completion of the shell. Similarly to other gold nanoparticles, gold–silica nanoshells have been studied specifically for their potential as imaging contrast agents with darkfield microscopy, two photon microscopy, reflectance confocal microscopy, and optical coherence tomography (OCT). In addition to having utility in cancer imaging, nanoshells that are strong absorbers can induce cancer cell death by converting light into heat. Silica-based gold nanoshells have been tested *in vitro* as targeted-therapy probes for human breast, prostate, brain, and liver cancers. In addition, nanoshells have demonstrated *in-vivo* therapeutic efficacy against xenografted subcutaneous tumors in mice and all grafted tumors in dogs.

The larger size of gold–silica nanoshells as opposed to many other gold nanostructures provides an advantage in scatter based imaging, but *in-vivo* delivery may be more challenging than for smaller particles in some applications

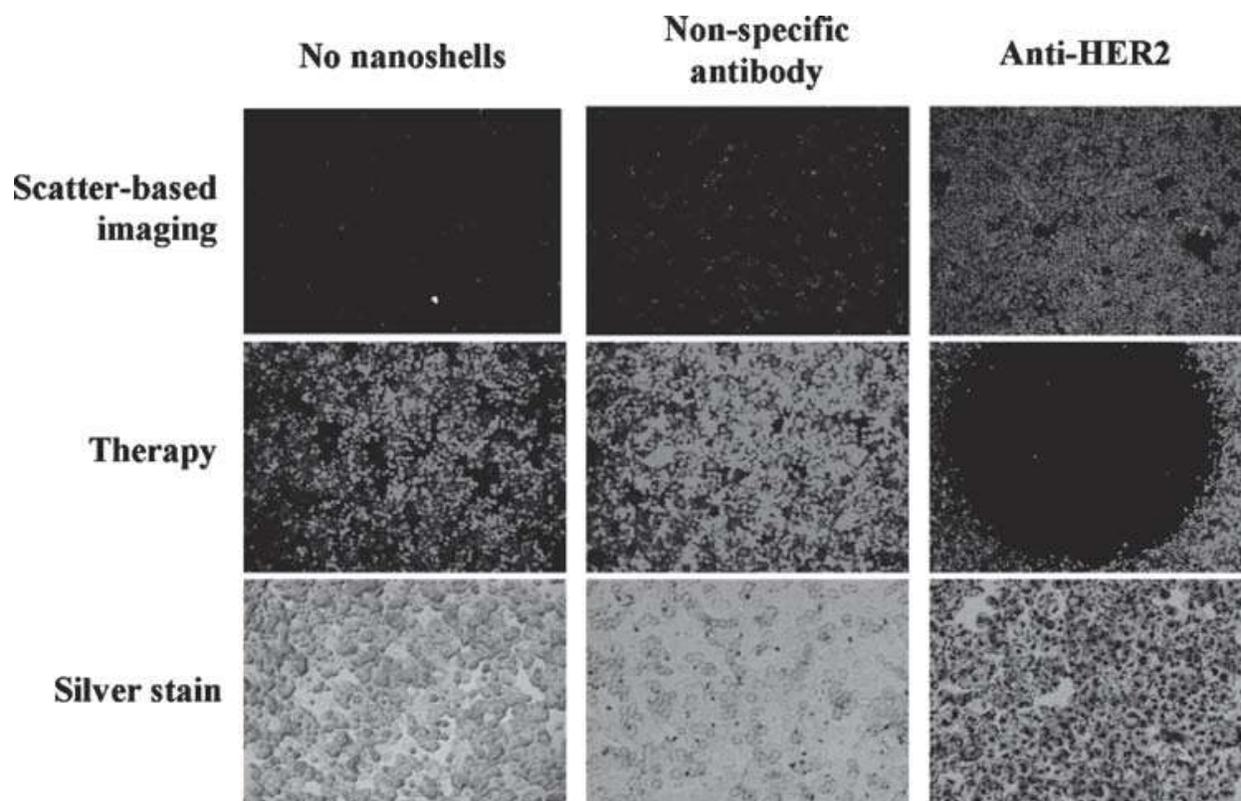


Figure 6. In-vitro imaging and therapy of human epidermal growth factor receptor 2 (HER2)-positive breast cancer cells using anti-HER2-conjugated

gold–silica nanoshells. The top row is darkfield microscopy of each treatment group, the middle row is a live stain of the cells after irradiation with NIR light, and the bottom row is a silver stain to show nanoshell binding. The same nanoshells are utilized to both image and ablate the breast cancer cells. Reproduced with permission.

Gold Colloidal Nanospheres

The final group of gold nanoparticles discussed for hyperthermia applications are gold colloidal nanospheres. Previously, these solid gold spheres were solely investigated for their use as imaging probes. However, the small size and relatively simple synthesis of these particles make them needed as the portion of incident light being converted into photothermal power by the nanoparticle, varied by less than factor of three between the different particles studied. This finding suggests that no particular nanoparticle configuration has significant therapeutic advantage over the others. While there has been significant focus to date on identifying ideal gold nanoparticle configurations for photothermal therapy, there are several additional promising research avenues for further optimization of the technology. The use of NIR light and nanoparticle absorbers in photothermal therapy offers critical advantages, particularly in protecting healthy tissue from thermal damage. However, solid tumors occur within the body at depths greater than 1 cm, which is beyond the penetration of NIR light in tissue. In these cases, fiber-optic probes often can be used to deliver light. In addition, the use of alternative irradiation modalities is an area of recent significant research activity and may be particularly useful for treating tumor locations that are difficult to access from the surface or through interstitial fiber-optic devices.

Second area of current research activity is the optimization of the delivery and bio distribution of gold nanoparticles *in vivo*. To ensure therapeutic success, maximal gold nanoparticle accumulation in the tumor is highly desirable. Furthermore, minimization of gold-nanoparticle accumulation within non target organs such as the liver and spleen is ideal. The use of smaller nanoparticles enhances the blood half-life and improves tumor accumulation and specificity. However, it is likely that additional modifications beyond size optimization would be useful to further improve nanoparticle biodistribution, and this has become an area of expanding research. A final area of current research activity is the identification of any impact of the long-term presence of gold nanoparticles *in vivo*. Relatively short-term studies have been performed to date with highly encouraging results. The remaining sections of this review will focus on discussing these areas of current.

Surface Enhanced Raman Scattring (SERS)

One advantage of gold nanoparticles is the simplicity of modifying the nanoparticle surface. By adding an antibody or other small molecule to the nanoparticle surface that corresponds with the targeted cancer, it has been suggested that the specificity of tumor accumulation and tumor cell specific binding could be increased. There have been many in-vitro studies supporting this hypothesis. Loo et al. were the first to demonstrate increased specificity of binding, darkfield imaging, and photothermal therapy in vitro using gold-silica nanoshells modified with an antibody to the HER2 receptor, which is overexpressed in some breast cancers. The El-Sayed group subsequently demonstrated in-vitro cancer ablation using anti-EGFR-conjugated gold nanorods. The specificity of antibody-targeting for therapy has been demonstrated with several other antibodies in vitro, including antibodies for acute lymphoblastic leukemia, *Pseudomonas aeruginosa*, and medulloblastoma. Similar to tumor-specific antibodies, small molecules specific for cancer cells have also been added to the surface of gold nanoparticles based on the hypothesis that these molecules will diffuse through tissue more efficiently than antibodies because of their small size. Using folate-conjugated nanorods, Tong et al. demonstrated that more laser power was required to kill cells with internalized nanorods versus cells with surface-bound nanorods in vitro. This was also demonstrated using gold nanorods conjugated to modified deltorphin peptide. Other groups have used targeting moieties such as bombesin to specifically target breast and prostate cancers for imaging, arginine-rich peptides to promote specificity via nanoparticle internalization by the target cells, and aptamers.

Despite the many in-vitro therapy demonstrations using surface-modified nanoparticles, in-vivo studies have not shown widespread success in enhancing delivery. Eghtedari et al. compared PEG- and anti-HER2-PEG-coated nanorods administered to tumor-bearing mice. They presented qualitative data in the form of histology to confirm that the addition of the antibody on the nanoparticle surface improved tumor accumulation. Li et al. combined gold nanorods targeted to either the HER2 or EGFR receptor and photoacoustic imaging to show that targeting enhanced the image contrast of squamous. For in-vivo targeting of the tumor vasculature, the use of phage technology is proposed. Bacteriophage (phage) display libraries have been used to identify peptide ligands that specifically bind the integrins, proteoglycans, and other features unique to blood vessels undergoing angiogenesis.

These phages can be selected and used to target tumor blood vessels for imaging or drug delivery. In addition, when coupled with gold colloidal nanospheres, gold-phage hydrogels have been imaged using darkfield microscopy, fluorescence microscopy, and NIR surface-enhanced Raman

scattering spectroscopy. By coating the primary particles described by Tasciotti *et al.* with phases specific to angiogenic blood vessels, the primary particles could be targeted to the tumor vasculature for Margi nation, adhesion, and, ultimately, delivery of therapeutic particles. The tumor could be identified and imaged using the gold–phage hydrogel coatings of the silicon microparticles, and then treated using the delivered nanoparticles, giving these vehicles theranostipotential.

Another vehicular strategy that has been demonstrated in the literature is the aptly named “trojan horse” method Gold–silica nanoshells were internalized in macrophages by incubating the particles with the cells for 24 hand allowing uptake via phagocytosis. The nanoshell-loaded macrophages infiltrated tumor spheroids in vitro after 3 days of incubation and accumulated at the rim of the spheroid ‘score hypoxic region. Although this was not a significant enhancement of tumor core penetration, there was a marginal increase in the percentage of gold nanoparticles reaching the hypoxic core. Although the in-vitro studies for both of these delivery strategies show some promising results, there have been no in-vivo studies delivering gold nanoparticles to date. In reality, no strategy discussed in this section has conclusively

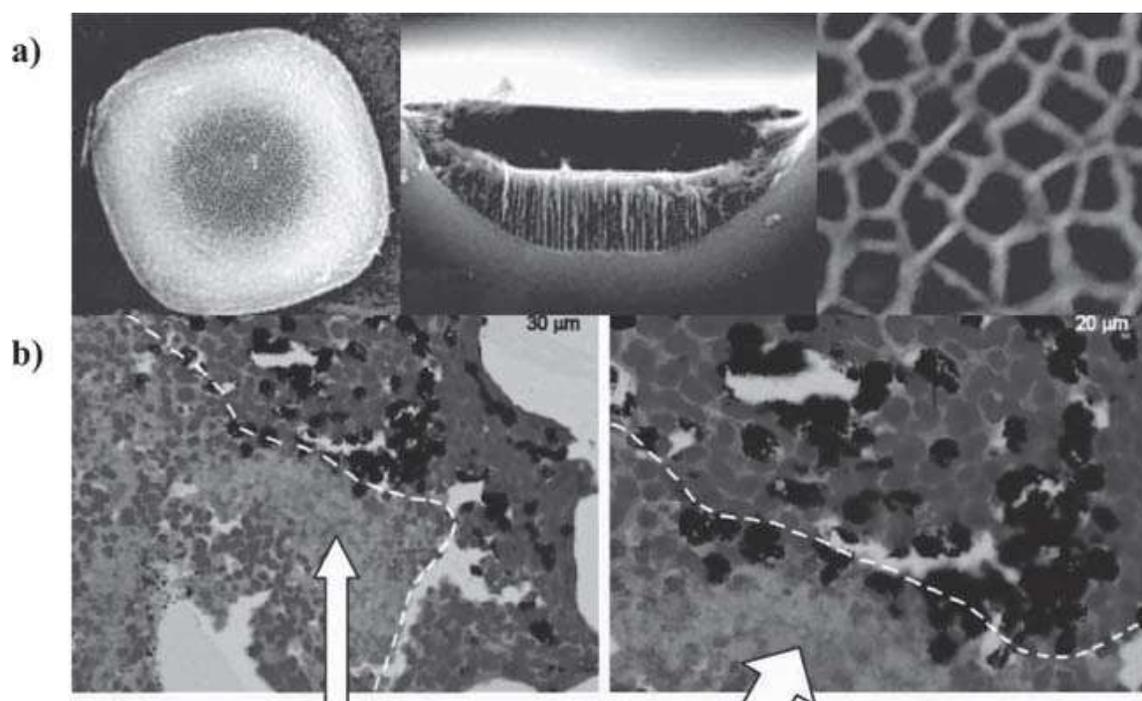


Figure.-7 SERS

Goodman *et al.* tested the effect of cationic (ammonium functionalized) and anionic (carboxylate-functionalized) 2 nm gold nanoparticles at different concentrations for 24 hand found that cationic nanoparticles were more cytotoxic than the anionic. Although cytotoxicity has been seen for gold nanoparticles of 5 nm at concentrations in the micromolar range, most gold nanoparticles used for

therapy applications are larger than 25 nm, where the IC₅₀ concentrations are several orders of magnitude larger. In addition, for most biological applications, the particles are PEGylated, which provides stability and protects cells from interacting with any surface detergents used to stabilize the nanoparticle.

Properties Of Cancer Shells

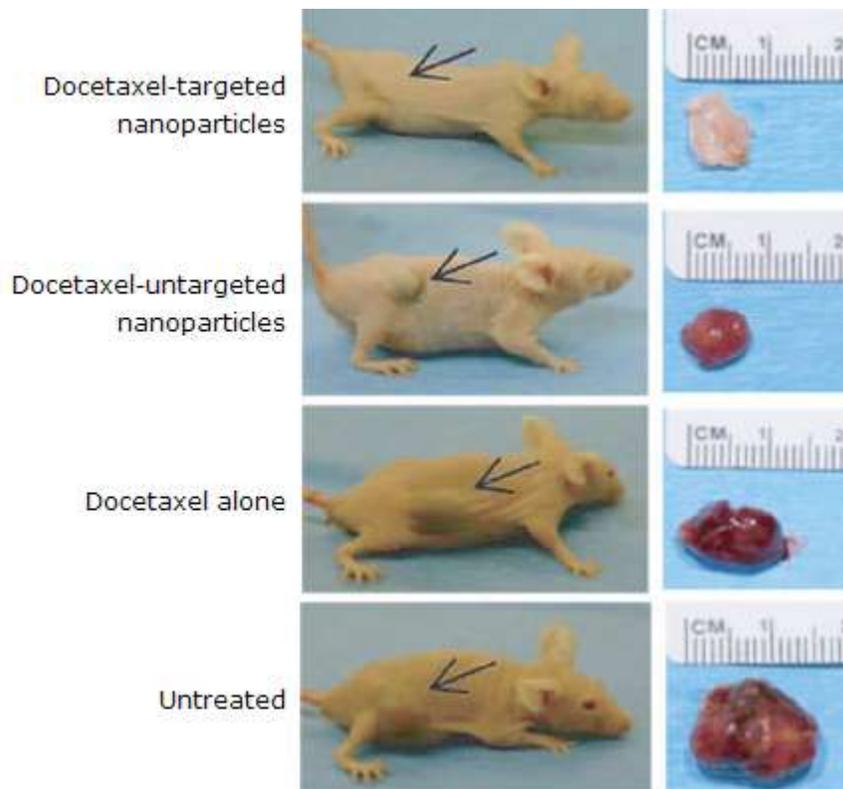


Figure-8 Experiment on mice bearing human prostate tumors

- Epidermal Growth Factor Receptor (EGFR) over expression and over activity have been associated many different types of Cancer.
- Cancer cells have a unique properties that can be exploited by nanoparticles Their rapid rate of growth causes them to intake an abnormal amount of nutrients (i.e., folic acid).
- Nanoparticles can be used to target bio-markers or antigens that are highly specific to Cancer cells.

Applications of Gold Nanoparticles of Cancer¹⁹

Gold nanoparticles has been successfully used as a therapy for

- Rheumatoid arthritis
- Alzheimer's disease
- The administration of hydrophobic drugs require molecular encapsulation and it is found that nanosized particles are particularly efficient in evading the reticuloendothelial system.

- Cancer detection

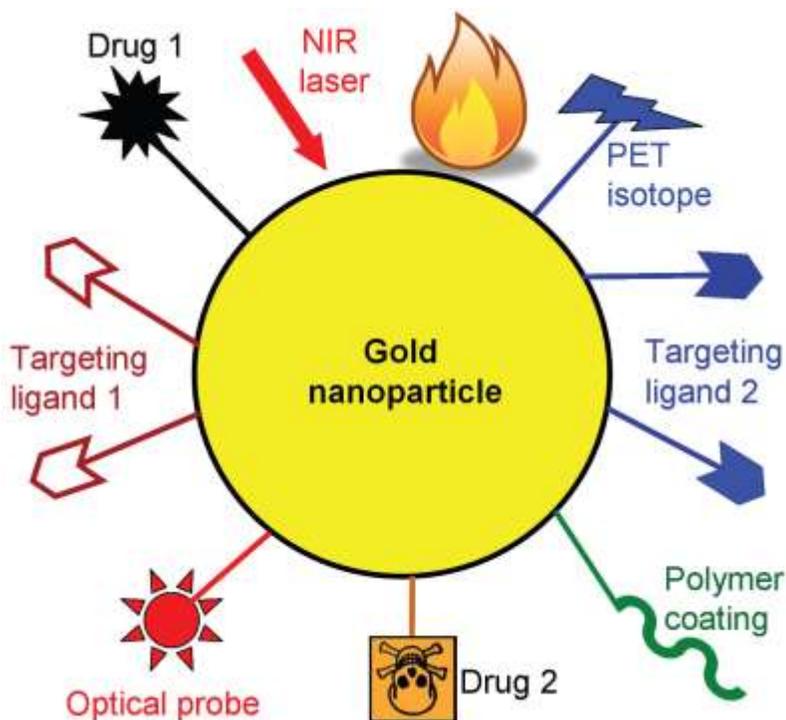


Figure 9: .multifunctional gold nanoparticle-based platform incorporating multiple receptor targeting, multimodality imaging, and multiple therapeutic entities. Not all functional moieties will be necessary and only suitably selected components are needed for each individual application

Background By Cancer²⁰

Cancer is the third leading cause of death (after heart disease and stroke) in developed countries and the second leading cause of death (after heart disease) in the United States .Because of the high death rate caused by cancer, plenty of research is going on in the field of Nanomedicine for Cancer diagnosis and therapy.

Tumor: Definition and Causes

Definition :-“Tumor is an abnormal growth of body tissue. It can be cancerous (malignant) or non-cancerous (benign)” .

Causes:-Generally tumors occur when there is a problem with the division of cells inside our body. Normally, the division of cells in the body is strictly .controlled If the balance of cell division and death is altered, a tumor may form.

Problems with the body's immune system can lead to tumors. Tobacco causes more deaths from cancer than any other environmental substance. Other causes include:

- Benzene and other chemicals and toxins
- Drinking excess alcohol
- Excessive sunlight exposure
- Genetic problems
- Inactivity (sedentary lifestyle)
- Obesity
- Radiation [2].

A cancerous cell surrounded by healthy tissue will reproduce at a higher rate than the other cells, thereby affecting the nutrient supply and elimination of metabolic waste products. Once a small tumor mass is formed, the healthy tissue will not be able to compete with the cancer cells as there is no sufficient supply of nutrients from the blood stream. Tumor cells will displace healthy cells until the tumor reaches a diffusion-limited maximal size. This diffusion limited maximal size of most tumors is around 2 mm. Generally tumor cells do not initiate apoptosis (a cell suicide mechanism) in a low nutrient environment as they do require oxygen, glucose and amino acids (building blocks of cell function). The healthy tissue which then becomes extinct did not demand high nutrients due to its slower growth rate. Thus the tumor cells will continue dividing because they do so without regard to nutrient supply but at the same time many tumor cells will also perish due to insufficient nutrients.

The tumor cells at the outer edge of a mass have the best access to nutrients while cells on the inside die creating a necrotic (death of cells) core within tumors that rely on diffusion to deliver nutrients and remove waste products. In essence, a steady state tumor size forms, as the rate of proliferation is equal to the rate of cell death until a better link with the circulatory system is created. To grow beyond this size, the tumor must recruit the formation of blood vessels to provide the nutrients essential to fuel its continued expansion. shows the tumor development from a single cell to a diffusion-limited tumor.

There can be numerous tumors at this diffusion-limited maximal size throughout the body. Until the tumor can gain that admission to the circulation it will remain at this size and the process can take years. The exact molecular mechanisms that initiate angiogenesis (growth of new blood vessels from preexisting blood vessels) at a tumor site are not known and could be unique to the site of origin but more information about what factors play a role in this process is being discovered .

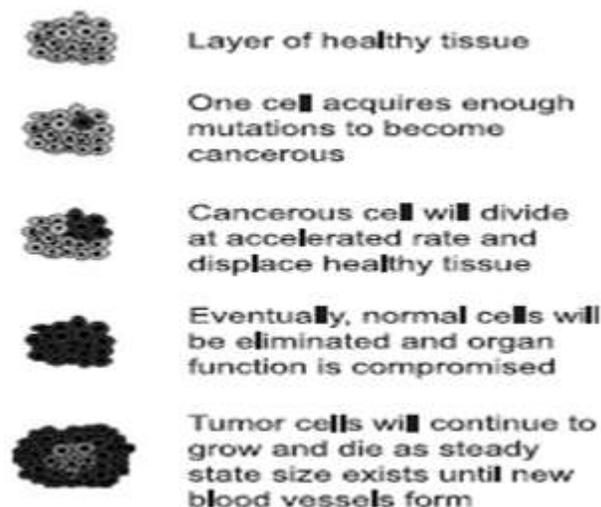


Figure 10: Tumor development from initial carcinogenesis to diffusion-limited maximal size

Current Cancer Treatments

There are different types of treatment for patients with cancer. Some of the standard treatments used are discussed as follows :

Surgery

Among all the treatments Surgery is the oldest form of cancer treatment. It as well plays an important role in diagnosing cancer and finding out how far it has spread (this process is called staging). For many types of cancer, surgery offers the greatest chance for cure.

This works best, especially for cancers that have not spread to other parts of the body. Majority of the people with cancer will have some kind of surgery. Preventive surgery: Preventive surgery is done to remove body tissue that is likely to become cancer, even though there are no signs of cancer at the time of the surgery. At time preventive surgery is used to remove an entire organ when a person has an inherited condition that puts them at a much higher risk for having cancer some day. For example, some women with a strong family history of breast cancer have a higher risk of getting breast cancer. In such cases, these women may want to consider prophylactic mastectomy i.e. the breasts are removed before cancer is diagnosed.

Radiation Therapy

Radiation therapy is a cancer treatment that utilizes high-energy x-rays or other forms of radiation to kill cancer cells or keep them from growing. There are two types- of radiation therapy

- 1) External radiation therapy and
- 2) Internal radiation therapy. In External radiation

therapy a machine is used outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The way the radiation therapy is given depends on the type and stage of the cancer being treated.

Chemotherapy

Chemotherapy is a type of cancer treatment where drugs are used to stop the growth of cancer cells. These drugs either kill the cancer cells or prevent them from dividing. Chemotherapy is taken by mouth or by injecting it into the vein or muscle. These drugs go through the bloodstream and can reach cancer cells throughout the body. This is known as systemic chemotherapy. When chemotherapy is given directly into the spinal column, an organ, or a body cavity such as the abdomen, the drugs primarily affect cancer cells in those areas. This is known as regional chemotherapy.

Hormone therapy

Hormone therapy is a recently used treatment for cancer. In this type of treatment either the action of hormones are blocked or removed to stop the cancer cells from growing. Hormones are substances generated by glands in the body and circulated in the bloodstream.

Immunotherapy

Another recently used treatment for cancer is Immunotherapy. In this, patients are given medication to stimulate the body's immune system to fight cancerous cells.

Limitations on Current Cancer Treatments

All cancer treatments come with benefits, risks, and side effects. The types and intensity of side effects differ from person to person and with the type and location of the cancer, and the person's health. Downside of the current cancer treatment methods are discussed below

1. Radiation therapy Limitations

As radiation is a local treatment, side effects depend on the area of the body being treated. Some of the most common side effects are minor burns, skin changes, fatigue, loss of appetite, nausea, vomiting, weakness, and lowered resistance to infections

2. Cancer Surgery Limitations

Common side effects of cancer surgery are: pain, swelling around the site of surgery, bleeding, bruising around the site of surgery, infection, fatigue, loss of appetite, etc.

3. Chemotherapy Limitation

Following are the common chemotherapy side effects that are common to several classes of chemo agents: nausea and vomiting, hair loss, fatigue, reduced blood levels of red blood cells, white blood

cells or platelets, reduced or absent menstruation (periods) in women, changes in thinking and memory, sore and inflamed throat and mouth, brittle or discolored nails, diarrhoea or constipation, etc. Some long term side effects could be permanent organ damage to heart, lung, liver, kidneys, or reproductive system. In some people cognitive functions (such as thinking, concentrating, and memory) remain a challenge even after months or years after treatment. In addition, nervous system changes can develop months or years after the treatment.

4.Hormone Therapy Limitations

In Hormone therapy certain drugs have a high risk of developing a blood clot. Hormonotherapy for prostate cancer can cause impotence. Hormone treatment for breast cancer can cause hot flushes and abnormalities in menstruation.

5. Immunotherapy Limitations

Some of the common immunotherapy side effects include itches and irritation around the injection area. Some other less common immunotherapy side effects are major swelling, bruising, cold, asthma or hay fever symptoms in a few hours after the injection and increased tiredness in the proceeding days after having the injection.

In the recent years, Gold nanoparticles (AuNPs or GNPs) have been brought to the front position of cancer research because of their simplistic synthesis procedures, rich surface chemistry, strongly enhanced and tunable optical properties and exceptional biocompatibility. High quality, yield and size controllable AuNPs can be prepared from simple citrate reduction method. We can also make different shapes of AuNPs like gold nanorods, gold nanoshells, hollow gold nanoparticles etc. These different shaped AuNPs show large red shift properties, thereby making them favorable candidates for Cancer Therapy .

Uses in Treatment²¹

Cancer cells die at 42° C (108° F), normal cells die at about 46° C (115° F)

Current optical fiber treatment Hollow, gold nanospheres are 50 times more effective at absorbing light near the infrared than solid gold nanoparticles can be tuned to be excited only by certain ranges of light In another study, pre-clinical trials reveal that a single intravenous nanoparticle injection eradicated 100 percent of tumors in mice when exposed to near-infrared light. Most work is being done with near-infrared light, which is harmless to humans but can only penetrate human tissue about 1.5 inches. Nanoparticles heated upto 70° C (160° F)The Kanzius RF Machine uses radio waves for dielectric heating



Figure 11 Kanzius RF Machine

Future Research And Scope²²

Human clinical trials within the next 2-3 years. Highly specific team of communicating multifunctional nanoparticles used in the discovery, treatment, and prevention of Cancer growth Safer, more consistent, and highly specific nanoparticle production Turning Cancer into a chronic, but manageable disease within the next 15-20 years.

There has recently been a great deal of interest in the scientific community concerning the application of nanotechnology in medicine. One particularly exciting field of research involves the use of gold nanoparticles in the detection and treatment of cancer cells (Soppimath, Betageri, & Cho, 2008). Current methods of cancer diagnosis and treatment are costly and can be very harmful to the body. Gold nanoparticles, however, offer an inexpensive route to targeting only cancerous cells, leaving healthy cells untouched. The unique light absorption and emission characteristics of gold nanoparticles have made them one of the most studied entities in recent cancer diagnostic research. Research has found that, when gold nanoparticles are subjected to light, the light is scattered in a highly specific pattern. These specific patterns are determined by the orientation of the nanoparticles.

The diagnosis of cancer is an area in which the light absorption and emission characteristics of gold nanoparticles have become a key advantage. It has been proposed that these aspects of gold nanoparticles themselves can be utilized in the diagnosis of cancer currently developing technique involves attaching a specialized antibody that is attracted to cancerous cells to the end of a gold

nanoparticle, and mixing this compound with blood or tissue samples containing cancerous cells. The blood or tissue samples are then subjected to white light and examined using standard microscopy. Since each type of cancer has a unique protein on its cell surface, the gold nanoparticles will be oriented differently, depending on which type of cancer cells they have been attached to. This results in each type of cancer having its own unique pattern of scattered light. Doctors would then be able to determine both the location and type of cancer with this method. Gold nanoparticles have a high usability level when compared to other similar methods of cancer detection.

One of these other methods employs quantum dots instead of gold nanoparticles to illuminate the location of cancerous tissue. The problem with these quantum dots, however, is that they burn out after extended exposure to light. Gold nanoparticles, on the other hand, will not burn out after extended light exposure, allowing them to illuminate cancerous cells for much longer periods of time than the quantum dots. Gold nanoparticle luminescence is also a more highly sensitive technique, permitting doctors to use fewer chemical markers in order to obtain the same information. As well as being able to diagnose cancer, gold nanoparticles have the potential to treat cancer without any of the harmful side effects associated with current treatment methods. Two of the most common forms of cancer treatment, chemotherapy and radiation therapy, are both extremely aggressive and can have fatal side effects even on young and otherwise healthy individuals. Side effects with these treatments occur because healthy cells are killed along with diseased cells in an effort to rid the body of cancer.

Two very promising methods of cancer treatment involving gold nanoparticles are currently being investigated for their ability to target only cancerous cells while leaving healthy cells unharmed. The first method utilizes gold nanoparticles to absorb light in the near-infrared wavelength range and the second involves a synthesis of chemotherapy and gold nanoparticles. The first possible method of treatment is based on gold nanoparticles that have either a trigonal pyramidal or star shape. These specific shapes are extremely efficient at absorbing near-infrared light and turning it into heat. The proposed procedure is to attach a cancer-attracted protein to these triangular or star-shaped gold nanoparticles in order to have the nanoparticles “stick” to the cancer cells, as they do in the cancer detection method. Meanwhile, they have no interaction with healthy cells.

Once the gold nanoparticles are attached, the cancerous location is subjected to a highly concentrated beam of near. infra-red light from an external source. This combination will cause the gold nanoparticles to heat up enough that they will actually ‘cook’ the cancerous cells. Even though the cancerous cells will be destroyed, there will be little or no damage to surrounding cells

since the infra-red light is harmless to any cells without an attached gold nanoparticle. Although this method is completely non-invasive, it does require the cancer to be relatively near to the surface of the patient's body in order for the gold nanoparticles to absorb enough of the light to kill the cancer cells. This method is a technologically evolved form of a procedure that is currently being used called photo ablation therapy (PAT). Unfortunately, current PAT techniques use such high frequency lasers to burn cancerous cells that they are very dangerous to the skin of the patient and are not always a viable option. Overall, the effectiveness, inexpensiveness, and safety of using gold nanoparticles make them an ideal candidate for use in next generation PAT.

The other method involving gold nanoparticles that scientists are hoping to use in the treatment of cancer is their synthesis with chemotherapy. In 2007, scientists found that gold nanoparticles in the shape of 'nanorods' were able to penetrate the cell membrane. They wanted to use this technology to help deliver chemotherapy in small doses directly to cancer cells, as opposed to subjecting the entire body to harmful chemotherapy. Unfortunately, this proved to be an ineffective delivery method due to the nanorods being too bulky for sufficient cell membrane penetration. More recently, in 2009, scientists fabricated a gold nanoparticle in the shape of a sphere. This new shape greatly increased the rate of cell penetration by the nanoparticles when compared to the larger and less agile 'nanorods'. Chemists used this new discovery to pair spherically shaped gold and iron oxide nanoparticles together into a 'dumbbell' formation, attaching a cancer-detecting molecule on one side and a cancer fighting molecule to the other.

Cisplatin, a powerful anticancer drug, is fixed to the gold nanoparticle, and Herceptin, an antibody that specifically seeks out breast cancer cells, is applied to the iron oxide. Once the Herceptin end of the compound locates a cancer cell, the spherical gold nanoparticle is able to penetrate the membrane and enter the cell, taking the small Cisplatin molecule along with it. As the gold-Cisplatin nano compound enters the cell, the sudden drop in intracellular pH causes the Cisplatin molecule to be hydrolyzed and separated from the gold nanoparticle. The cancer cell is now treated internally so as not harm any of the surrounding cells. Although this test was specifically targeted at breast cancer using Herceptin, the same technique can be employed against any type of cancer as long as it has an active antibody. As with the other treatment method, the appeal of this technique is that the cancer treatment can be applied locally and non-invasively, and has the ability to not only treat the cancer, but detect and illuminate it as well.

Nanoscience has had a huge impact in medicine in recent years due to its non-invasive applications. The use of gold nanoparticles to diagnose and treat cancer has been, and will continue

to be, on the forefront of this exciting research. While cancer detection using gold nanoparticles in common medical practice is just around the corner treatment using gold nanoparticle photothermal ablation and nano-chemotherapy will be in clinical trials for some time before they are being used on patients regularly. With nanotechnology advancing as fast as it currently is, scientists will hopefully be able to utilize the characteristics of compounds such gold nanoparticles in the detection and treatment of many more deadly diseases in the years to come.

SUMMARY²³

Metastasis is still an extremely complex disease with multiple questions still remaining. While 90% of human cancer deaths are due to cancer metastases, the hope for fighting cancer is sustained by the fact that there were more than 50 new agents approved in the past 10 years for cancer treatment and hundreds of new agents in clinical development. The development of nanoparticle drug delivery systems is expected to have a big impact on the clinical approaches for cancer therapy. The ability to specifically target nanoparticles along with the controlled delivery of a therapeutic payload provides powerful new ways to treat cancer which are only starting to be realized. By rationally designing nanoparticles based on improved knowledge of cancer biology and the tumor microenvironment, improved efficacy can be achieved. In addition, multifunctional nanoparticles able to carry imaging agents and deliver multiple drugs are now being developed for enhanced detection and treatment of cancer. The application of nanotechnology to cancer has already produced some exciting results and holds even greater promise for cancer patients in the future.

Plasmonic gold nanostructures thus show great promise for the selective PTT for cancer as well as other diseases. We propose the name PPTT for this treatment. It is realized that number of variables need to be further addressed, e.g., stability, biocompatibility, and chemical reactions of nanoparticle bioconjugates in physiological environments, blood retention time, tumor extravasation, the fate of the nanoparticles following therapy, etc. We anticipate that the success and promise of the initial use of plasmonic nanoparticles for selective PPTT could be efficiently extended to clinical stage once the optimal parameters of these variables are identified, as is being done through -Different types of Cancer cells have unique properties that can be exploited by nanoparticles to target the Cancer cells-Nanoparticles can be used to detect/monitor (by utilizing or adding optic, magnetic, and fluorescent properties) and to treat Cancer (by Heat ablation, chemotherapy, gene therapy).-No human trials have been performed yet and human trials are still

atleast a few years away. (Unknown side effects, toxicity, difficulty in manufacturing and harmful by products, need for highly specific nanoparticles) Multifunctionality is the key advantage of nanoparticles over traditional approaches. Targeting ligands, imaging labels, therapeutic drugs, and many other functional moieties can be integrated into the nanoparticle conjugate to allow for targeted molecular imaging and molecular therapy of single modality is perfect and sufficient to obtain all the necessary information for a particular question . For example, it is difficult to accurately quantify optical signal in living subjects, particularly in deep tissues; Radionuclide-based imaging techniques (eg, positron emission tomography [PET]), are very sensitive and highly quantitative but they have relatively poor spatial resolution.

CONCLUSION

Combination of certain imaging modalities can offer synergistic advantages over any single modality alone . Dual-modality agents that combine PET, which is very sensitive and highly quantitative (Phelps 2000),and optical imaging, which can significantly facilitate ex vivo validation of the in vivo data, should be of particular interest for future biomedical research. The relatively large size of the gold nanoparticle may potentially allow for simultaneous multiple receptor binding of the targeting ligands on the same particle. Thus, targeting multiple closely-related with in vivo diagnostics (non-invasive imaging before, during, and after treatment) can provide a synergistic approach that neither strategy alone can offer. Upon further development and validation, nanoparticle-based approaches (both ex vivo nano sensors and in vivo imaging) will eventually be able to predict which patients will likely respond to a specific molecular therapy and monitor their responses to personalized therapy. With the capacity to provide enormous sensitivity, throughput, and flexibility, nanotechnology has the potential to profoundly impact cancer diagnosis and patient management in the near future. Big strides have been made and many proof-of-principle studies have been successfully performed, the future looks brighter than ever yet many hurdles remain to be conquered.

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